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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,022	09/17/2003	Dennis M. Klinman	4239-66899	7954

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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
04/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,022	KLINMAN ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8-21 and 25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-21 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to communication filed 1/4/2010. Claims 1, 2, 4-6, 8-21 and 25-34 are under current examination.

Any rejection(s) and/or objection(s) not reiterated herein have been withdrawn.

To allow entry of the rejection(s) set forth herein, the instant office action is non-final.

Response to Arguments

Applicant's arguments, see Remarks, p. 19-24, filed 1/4/2010, with respect to the rejection(s) of claim(s) 1, 2, 4-6, 8-22 and 25-34 under 35 USC 103, *incorrectly* using Klinman et al. (WO 00/61151) as an equivalent to US Patent 6077245 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Klinman et al. (WO 00/61151) using properly cited passages of this reference. Other arguments are addressed below.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 6, 8-15, 21, 26, 27 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151-IDS), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000).

The claims are drawn to (in part): a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising:

Selecting an immunocompromised subject infected with a secondary infection;

Administering to the immunocompromised subject infected with the secondary infection a therapeutically effective amount of an immunostimulatory D ODN, wherein the D ODN is at least 18 nucleotides to about 30 nucleotides in length and comprises a sequence represented by the following formula:

5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3' wherein the central CpG motif is unmethylated, Pu is a purine, Py is a pyrmidine, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to10; and

Assessing the immune response to the secondary infection in the subject;

Thereby increasing the response to the secondary infection in the immunocompromised subject.

Klinman teaches a method of increasing an immune response in a subject using an immunostimulatory D oligonucleotide wherein the sequence is represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3' wherein

the central CpG motif is unmethylated (see Abstract and SEQ ID NO: 37 which fits this formula; see instant claim 1, *in part*). Note that the sequence set forth by SEQ ID NO: 37 of this prior art reference is as follows: ggtgcatcgatgcaggggg and this sequence meets the structural limitations of claim 8 (wherein N is 6) and claims 21, 26, 27, 39 and 31 (for both SEQ ID NO: 1 and SEQ ID NO: 177 of the instant specification). The author also discloses the use of a phosphorothioate which may occur at either termini of a sequence, including the last two or three 5' and/or 3' nucleotides (p. 3, lines 26+, p. 10, lines 7+, p. 14, lines 1+ and instant claims 12 and 13). Note that the phosphodiester bases as claimed in claims 9-11 are normal DNA phosphodiesterase linkages, i.e. without modifications (p. 13, line 12). Also see claim 3 of this reference, claiming a sequence wherein the sequence on the 5' side of the CpG sequence forms a palindrome with the sequence on the 3' side of the CpG sequence. This meets the structural limitation of claim 14 wherein X1X2X3Pu1Py2 and Pu3Py4X4X5X6 are self-complementary. Tables 1-3 provide the functional characterization of the sequences in the induction of an immune response. The author states that the disclosed invention can be used to treat prevent or ameliorate any suitable disease associated with the immune system, such as immune system deficiencies which include those diseases or disorders in which the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+).

While Klinman teaches the structure of the immunostimulatory sequence as claimed for the treatment of immune system deficiencies, Klinman does not teach a method of increasing an immune response to an *opportunistic infection in an*

immunocompromised subject having *SIV or AIDS* wherein the *secondary infection is a viral infection*.

Lu et al. describes opportunistic infections in SIV-infected Macaques (see abstract). The author states that "opportunistic infections are frequently found in AIDS patients and SIV challenged macaques" (see p. 921, col. 2). Table 1 provides a summary of opportunistic infections in macaques, including pneumonia, a viral infection (see instant claim 15).

Cho et al. describes the use of immunostimulatory DNA sequences containing unmethylated CpG motifs for stimulating host defense in subjects with chronic immunosuppression and AIDS (see abstract). Cho et al. provide that immunostimulatory DNA sequence-based vaccines have a clinical application in AIDS and other immunodeficiencies and these vaccines may provide protection against opportunistic infection (see p. 513, col. 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the CpG-containing sequences described by Klinman in a method for treating selected immunocompromised subjects with opportunistic infections and assessing the resulting responses. One of ordinary skill in the art at the time the invention was made would have been motivated to use a characterized immunostimulatory CpG sequence (as taught by Klinman) for the advantage of stimulating a host defense in AIDS, SIV and other chronic immunosuppression (see Cho and Lu). Separately, Klinman teaches that the disclosed methods could be used when the immune system is not functioning at normal capacity, or in which it would be

useful to boost the immune system response (p. 8, lines 19+) and this would motivate one of ordinary skill in the art to select immunocompromised subjects, including those with a secondary infection. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 5 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of US Patent No. 6326007 (Yilma) and Bielorai et al. (*Bone Marrow Transplantation*, 2000) and

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach a subject that is immunocompromised as a result of HIV-2 or chronic granulomatous disease.

Yilma describes HIV-2 as being associated with both immunodeficiency and opportunistic infections (see col. 1, lines 53+).

Bielorai et al. describes chronic granulomatous disease as a primary immunodeficiency disorder characterized by susceptibility to bacterial and fungal infections or opportunistic infections (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) having either HIV-2 or granulomatous disease using characterized CpG-containing sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of enhancing host survival in immunosuppressed subjects to provide protection against opportunistic infections (see Cho). Separately, Klinman teaches that the disclosed methods could be used when the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+) and this would motivate one of ordinary skill in the art

to select immunocompromised subjects, including those with a secondary infection. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4, 16, 25, 28, 29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of Raz (US Patent No. 6552006), Hamour et al. (J. Infect., 1998 ABSTRACT ONLY) and Glaser et al. (Clin. Infect. Dis., 1994 ABSTRACT ONLY).

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach treating secondary infections, specifically *Leishmania* and *Listera*, or HIV-1 infection.

Raz teaches immunomodulatory nucleic acids comprising CpG motifs enhance host survival against *Listeria* and *Leishmania* (col. 3, lines 34+; instant claims 16 and 28).

Hamour et al. discloses that *Leishmania* is a well recognized opportunistic infection in patients with the HIV-1 (see abstract).

Glaser et al. is cited to demonstrate that *Listeria* is a known opportunistic infection among HIV-infected subjects (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) to either *Listeria* or *Leishmania* using known CpG-containing sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of enhancing host survival against known opportunistic infections *Listeria* and *Leishmania* (see Raz). Separately, Klinman teaches that the disclosed methods could be used when the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+) and this would motivate one of ordinary skill in the art to select immunocompromised subjects, including those with a secondary infection. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 17, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al.

(*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of Davis et al. (*Vaccine*, 2000) and Chung et al (*Antivir. Chem Chemother.*, 2001 ABSTRACT ONLY).

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach treating hepatitis B as the secondary infection in an immunocompromised subject.

Davis et al. evaluated the immune response following CpG ODN administration and determined that CpG ODN greatly increased the titers of antibody against HBsAg in blood (see abstract, p. 1921, col. 2). Note that this meets the limitations of evaluating the immune response to hepatitis B antigen comprising determining the amount of antibodies to hepatitis B in the subject's serum (instant claims 33-34).

Chung et al. is cited to show that HBV infection is an HIV-associated opportunistic infection (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) to HBV using known CpG-containing sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of stimulating host

defense in immunocompromised subjects against known opportunistic infections including HBV. Further, the prior art teaches that CpG administration successfully increases antibody titers against HBsAg (see Davis et al.). Separately, Klinman teaches that the disclosed methods could be used when the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+) and this would motivate one of ordinary skill in the art to select immunocompromised subjects, including those with a secondary infection. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151), Lu et al. (*Vaccine*, 1997) and Cho et al. (*Nature Biotechnology*, 2000) as applied to claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 above, and further in view of Hamour et al. (J. Infect., 1998 ABSTRACT ONLY) and Fraternale et al. (*JAIDS*, 2000).

The combination of Klinman, Lu and Cho teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising administering immunostimulatory oligonucleotides, including a sequence represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3'.

The combination of Klinman, Lu and Cho does not teach a method of further administering HAART or AZT to subjects with HIV-1.

Hamour et al. discloses that *Leishmania* is a well recognized opportunistic infection in patients with the HIV-1 (see abstract).

Fraternale et al. describes antiretroviral therapies in HIV-1 patients, including HAART and AZT (see abstract and whole document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase an immune response in an immunocompromised subject (as taught by the combination of Klinman, Lu and Cho) having an HIV-1 infection using known CpG-containing sequences and known antiretroviral drugs, including HAART and AZT. One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the advantage of stimulating host defense in immunocompromised subjects against opportunistic infections and for the treatment of HIV-1 infection itself. Separately, Klinman teaches that the disclosed methods could be used when the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+) and this would motivate one of ordinary skill in the art to select immunocompromised subjects, including those with a secondary infection. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary

skill in the art. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 1/4/2010 have been fully considered but they are not persuasive. Arguments are found on p. 21+ of the Remarks. Applicant submits that that Klinman, Lu and Cho do not teach the steps of selecting an immunocompromised subject with a secondary infection and assessing the immune response to the secondary infection. Applicant acknowledges that Cho teaches that the disclosed vaccines "may have another clinical application in AIDS and other immunodeficiencies, which are characterized by reduced or absent Th function. These vaccines could induce effective cell-mediated immunity independent of T-cell help, providing protection against opportunistic infection" (p. 22). Note that this teaching provides motivation in selecting an immunocompromised subject with a secondary infection for the purposes of administering the CpG-containing ODNs as described by Klinman et al. Separately, it would be obvious to assess the resulting immune responses following the administration of *any* composition to a patient of *any* disease.

The argument of unexpected results (Remarks, p. 22-23) is not found persuasive for at least the reasons set forth above. Separately, it is noted that Applicant provides a limited example of unexpected results (SIV-infected macaques further infected with *L. major*) and this example is not commensurate with the scope of the claimed invention.

Conclusion

No claim is allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M. H./
Examiner, Art Unit 1648

/Zachariah Lucas/
Primary Examiner, Art Unit 1648